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Chemotherapy with or without High-dose Medroxyprogesterone Acetate in Oestrogen-receptor-negative Advanced Breast Cancer

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In a randomised study 142 patients with advanced oestrogen-receptor-negative breast cancer in the tumour tissue received chemotherapy alone or chemotherapy combined with high doses (1000 mg daily) of oral medroxyprogesterone acetate (HD-MPA). Of the 126 fully evaluable for response, the response rates were 46% for chemotherapy alone and 73% for chemotherapy with HD-MPA ($P = 0.005$). There was no significant difference with regard to duration of response. Of the 138 patients evaluable for survival and toxicity, survival was shorter in the combined treatment group; median survival of 9 versus 13 months ($P < 0.05$). Considerable toxicity was seen from HD-MPA, especially weight gain and fluid retention. The present study provides evidence that in concordance with preclinical studies an interaction between chemotherapy and HD-MPA may exist in breast cancer normally resistant to hormone therapy. The side-effects from MPA were substantial, however, and the survival data are of great concern.
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INTRODUCTION

SEVERAL STUDIES have indicated an increased response rate in advanced breast cancer when chemotherapy is combined with high doses of medroxyprogesterone acetate (HD-MPA) [1]. Receptor assays were not reported in these publications, and the response could merely reflect an additive effect, with some patients responding to chemotherapy and some to hormone therapy. Preclinical experimental data for a true interaction between chemotherapy and HD-MPA were been provided by Formelli *et al.* [2] who found that MPA could potentiate the effect of chemotherapy on a hormone insensitive subline of 13762 mammary adenocarcinoma in rats. This hypothesis can only be tested in a clinical setting by treating patients that are normally resistant to hormone therapy. There is abundant data demonstrating that breast cancer patients with oestrogen receptor contents <10 pmol/g protein (ER-) in the primary

tumour or metastatic tissue, have a response rate of <10% to endocrine treatment.

In the present multicentre study patients with ER- in primary or metastatic tissue were randomised to receive chemotherapy with or without additional HD-MPA.

PATIENTS AND METHODS

A total of 142 patients with advanced breast cancer were randomised during the period of May 1985 to June 1986. Receptor-status was measured in two laboratories. 4 patients were excluded (protocol violations, receptor positive or unknown, or not evaluable disease). 8 patients died before three cycles of chemotherapy had been given and are not considered evaluable for response. All of these patients were in the group that received MPA. Thus remains 126 fully evaluable patients with ER-tumours. In most cases receptor status was from the primary tumour. In 101 patients the progesterone receptor contents were also determined.

ER was measured by a standard dextran–charcoal method with 3_3-oestradiol as the ligand, essentially as recommended by European Organization for Research on Treatment of Cancer [3]. Results of the ER assay were given as picomoles binding capacity per gram cytosol protein (pmol/g; numerically equivalent to fmol/mg). In breast cancer, values ≥10 pmol/g are regarded positive if the equilibrium constant is satisfactory.

The quality of the receptor results was monitored by the inclusion of quality control samples in each run and by participation in the running EORTC European Quality Control Assessment of Steroid Receptor Assays, all giving fully satisfactory results.

A pretreatment initial white cell count (WCC) of ≥4 × 10^9/l and platelet count of ≥125 × 10^9/l were required. Patients with another type of neoplasm, or other medical conditions which could preclude adherence to the treatment or assessment schedule, were excluded. Metastases were measurable or evaluable. Patients with brain metastases, leptomeningeal affection or osteoblastic lesions as the only manifestation of the disease were excluded. All patients were previously untreated with systemic agents except for adjuvant chemotherapy given as part of the primary treatment.

Prior to initial treatment all patients underwent physical examination. Blood count, chest X-ray, bone isotope scan and/or bone survey radiographs and measurements of indicator lesions were obtained in all patients. If indicated by liver function tests, liver scan, ultrasound or computed tomography (CT) was performed. Brain scans and/or CT was performed in those patients who had symptoms or signs suggestive of central nervous system metastases.

Patients were allocated by random numbers to either chemotherapy alone or chemotherapy combined with HD-MPA. Due to changes in treatment policy during the accrual time 17 patients received vincristine 2 mg, doxorubicin 50 mg/m² and cyclophosphamide 600 mg/m² (VAC) every 3 weeks while the remaining patients were infused with 5-fluorouracil 1000 mg/m² on days 1 and 2 over 3–4 h followed on day 2 by mitomycin 6 mg/m² over 30 min (FuMi), repeated every 3 weeks. A maximum of 10 courses was given. The dose of MPA was 500 mg orally twice daily from start of and as long as chemotherapy was given (Table 1).

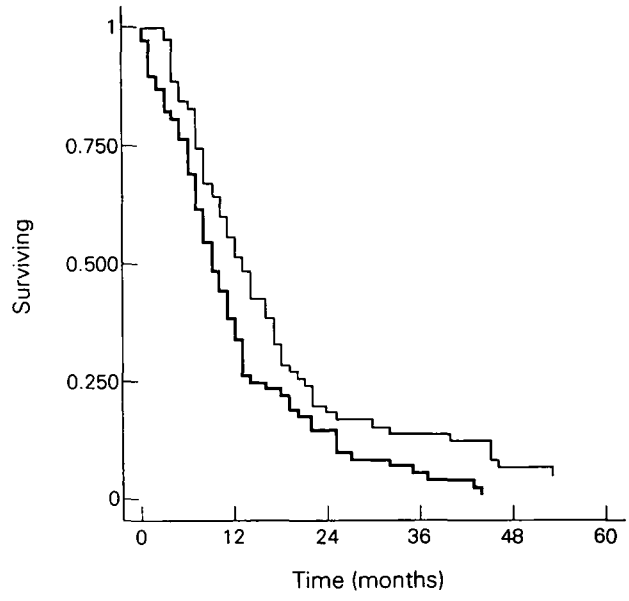

Fig. 1. Life table plot of survival from start of treatment for the two groups; chemotherapy alone (n = 70) and chemotherapy combined with HD-MPA (n = 68) in advanced breast cancer. . . . No MPA, n = 70; —— MPA+, n = 68, P < 0.05.

Blood counts were performed before each course, but nadir values were not determined. When WCC and/or platelet counts before start of treatment were between 3.9 and 3.0 × 10^9/l and 124 and 100 × 10^9/l, respectively doses of chemotherapy were reduced by 25% and for the corresponding values 2.9–2.0 and 99–75 × 10^9/l dose reduction was 50%. For lower values treatment was postponed one week. The dose was not escalated.

The allowed maximal cumulative dose for doxorubicin was 500 mg/m² and of mitomycin 100 mg (regardless of body surface area). Non-responding patients treated with VAC were treated with FuMi while most patients that received FuMi received weekly doses of doxorubicin as second-line [4].

The main characteristics of the patients are summarised in Tables 2 and 3. There were no significant differences between the two groups with regard to important prognostic factors.

The criteria used for evaluation were those recommended by UICC [5].

Table 1. Treatment regimens

Chemotherapy	
FuMi—5-fluorouracil 1000 mg/m² days 1 and 2 Mitomycin 6 mg/m² day 2 (max. cum. dose 100 mg)	every 3 weeks (n = 120)
VAC—Vincristine 2 mg Doxorubicin 50 mg/m (max. cum. dose 500 mg/m²) Cyclophosphamide 600 mg/m²)	every 3 weeks (n = 18)
Hormone therapy	
MPA 500 mg × 2 orally daily	

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Table 2. Main patient characteristics

	Chemotherapy (n = 70)	Chemotherapy + HD-MPA (n = 68)
Mean age (years)	55	56
Premenopausal	24	26
Postmenopausal	46	42
ER		
0	30	18
1–5	12	17
6–9	6	11
Values only given as + or −	22	22
Disease-free interval (mean, months)	21	17
Time from first metastases until randomisation (mean, months)	7	6

Table 3. Localisation of metastases (more than one localisation per patient)

	Chemotherapy (n = 70)	Chemotherapy + HD-MPA (n = 68)
Skeletal	22	28
Soft tissue	37	38
Visceral	46	42

Statistics

The comparability of the two treatment groups with respect to baseline variables was assessed by the χ^2 test for categorical variables and two-sample t-test for means. Survival curves were calculated by the Kaplan–Meier method, and significance was assessed by the log-rank method [6].

RESULTS

126 patients were considered fully evaluable for response, 67 in the chemotherapy alone group and 59 in the combined treatment group, and 138 (70 chemotherapy and 68 chemotherapy+HD-MPA) for survival and toxicity. 5 of the 138 patients had ovarian irradiation as adjuvant treatment while 38 had received adjuvant chemotherapy with CMF for 1 year (Table 4). None of the patients had received prior systemic treatment for metastatic disease. All patients were ER−. Among the 18 patients that received VAC, 8 also received HD-MPA. The response rate for chemotherapy alone was 31/67 (46%) (5/9 VAC, 26/58 FuMi) versus 43/59 (73%) (8/8 VAC, 35/51 FuMi) (P = 0.005) for chemotherapy+HD-MPA (Table 5). The difference in response (CR+PR) is 27%. Difference in response rate for FuMi+HD-MPA vs. FuMi alone was 24% (P = 0.004). Since patients were included according to ER and not PgR status some of the patients had PgR positive tumour tissue. Theoretically this could explain the difference in response rate for the two regimens. An analysis according to patients that had PgR determinations undertaken was therefore made (Table 6). Also for PgR- tumours the response rate was higher (70 vs. 46%, P = 0.08) for the group that received chemotherapy+HD-MPA. Response in the two treatment groups according to localisation, i.e. skeletal, soft tissue or visceral (lung, pleural or liver), of metastases was also analysed (Table 7). There was a tendency for skeletal metastases to respond best to the combined therapy. The median duration of complete remissions was 12 months in both groups, ranging from 4–28 months for patients on chemotherapy alone and 5–45 months for the combined

Table 4. Previous therapy

	Chemotherapy (n = 70)	Chemotherapy + HD-MPA (n = 68)
Surgery only	28	22
Surgery and castration	3	2
Surgery and local radiotherapy	13	11
Surgery and adjuvant chemotherapy	16	22
Local radiotherapy only	4	3
No previous therapy (advanced disease at admittance)	6	8

Table 5. Response to treatment

	Chemotherapy (n = 67)	Chemotherapy + HD-MPA (n = 59)
CR	5(46%)*	11(73%)*
PR	26	32
NC	21	9
PD	15	7

*P = 0.005.
CR = complete response; PR = partial response; NC = no change; PD = progressive disease.

Table 6. Response according to PgR

PgR (pmol/g protein)	Chemotherapy RR (%)	Chemotherapy + HD-MPA RR (%)
0–9	17/37 (46)	23/33 (70)*
>10	8/18 (44)	9/13 (69)
Unknown	6/12 (50)	11/13 (85)

*P = 0.08.
RR = relative response.

Table 7. Response to treatment by site

	Chemotherapy (n = 67)				Chemotherapy + HD-MPA (n = 59)			
Site	n	CR	PR	RR(%)	n	CR	PR	RR(%)
Skeletal	22	0	5	(23)	26	2	14	(62)*
Soft tissue	35	2	13	(43)	33	5	17	(67)
Visceral	44	3	17	(45)	36	7	15	(61)

*P = 0.01
Abbreviations as in Table 5.

Table 8. Toxicity

	Chemotherapy (n = 70)	Chemotherapy + HD-MPA (n = 68) (%)
Non-haematological parameters		
Cushingoid features	0	4 (6)
Metrorrhagia	0	2 (3)
Deep venous thrombosis	0	1 (1)
Cardiac failure	0	2 (3)
Serious withdrawal bleeding	—	1 (1)
Haematological parameters		
Mean WCC before planned cycle × 10^9/l	5.0	6.0
Range WCC	1.9–11.2	1.7–16.8
Mean platelets before planned cycle × 10^9/l	248	270
Platelet range	72–690	105–577

WCC = white cell count.

treatment. For partial remissions the median duration of response were 6 months in both groups (range 2–16 and 2–15).

The median survival in the chemotherapy alone group were 13 months versus 9 months ($P < 0.05$) in the combined treatment group (Fig. 1). There was no difference with regard to response to second line chemotherapy which was approximately 20% in both groups. 1 patient in each group responded to tamoxifen. One was a patient with local relapse and borderline value for ER (9 pmol/g protein) in the biopsied tissue. In this case tamoxifen was given as second line therapy. The other patient had intra-abdominal, probably lymph-node metastases (not histologically verified), and received tamoxifen after FuMi and weekly low-dose doxorubicin.

All VAC patients experienced severe nausea, vomiting and alopecia which was the main reason for the change in treatment policy during the accrual time for this study. The FuMi regimen was well tolerated and only a few patients had vomiting and alopecia (Table 8). Toxicity from HD-MPA was substantial, weight gain and fluid retention being the main problem experienced by about half of the patients when the treatment time extended beyond 3 months. 2 patients had clinical symptoms of cardiac failure that was felt could have been induced by MPA medication which was therefore stopped and the patients treated by diuretics. Both patients condition then improved, one of these patients is still alive after 2 years. The other presumably died from cancer. One patient had a life-threatening vaginal bleeding after anticoagulation for venous thrombosis and withdrawal of MPA medication. In fact, vaginal bleeding after MPA withdrawal was seen regularly, but serious bleeding was seen in this case only, probably due to the simultaneous anticoagulation. Vaginal bleeding during treatment was seen in only a few cases. All of the 8 patients that died before 4 weeks of treatment belonged to the CH+HD-MPA group. If these patients are included, the response rates are 64 (43/67) versus 46% (31/67) ($P < 0.05$). Retrospectively we have collected all available information on these patients, especially with regard to death possibly being related to MPA induced cardiovascular complications. 4 patients were autopsied. The cause of death in these cases was disseminated breast cancer without evidence of pulmonary emboli or cardiac failure. 2 patients with lung metastases had fever prior to death and cause of death was stated to be pneumonia, clinically without evidence of serious cardiovascular disease, while 2 patients died from disseminated disease without clinical evidence of cardiovascular complications.

No significant difference in WCC and platelet counts before planned courses was registered. Nadir values were not measured.

DISCUSSION

The two groups of patients were well balanced according to age, disease-free interval and time from first metastases to randomisation.

There was a significantly higher response rate in the group of patients that received HD-MPA in addition to chemotherapy. There was a tendency for skeletal metastases to respond best to the combined therapy, but great caution should be taken in any interpretation of data from subgroups, especially keeping in mind the difficulties associated with evaluation of response in bone. Duration of response did not increase by the addition of HD-MPA to chemotherapy. However, due to the early death of 8 patients in the combined treatment group, survival was worse in the chemotherapy + HD-MPA group. We have no evidence that these patients died from cardiovascular disease. Considerable side-effects from HD-MPA were seen, especially weight gain and fluid retention. Detailed recording of body weight was not undertaken and more exact data can therefore not be given. In 2 cases manifest cardiac failure was probably elicited by HD-MPA. In one case withdrawal of MPA in a patient that was anticoagulated resulted in serious vaginal bleeding. All responses were indicated after the first course and all, also complete responses, obtained within the first three courses. Since no patients had delays between the first three courses, the increase in response rate cannot be attributed to a bone-marrow protective effect. Moreover, there was no significant difference in WCC or platelet counts before planned courses between the two treatment groups. It is of some concern that the chemotherapy regime was changed during the trial. There is an indication that the doxorubicin regimen profitted the most by addition of HD-MPA. Considering the few patients that received VAC this is somewhat speculative. However, most of the experimental data concerns the combination of doxorubicin and MPA. A new protocole combining doxorubicin and MPA has therefore been activated.

Since patients were selected on the basis of lack of ER receptors it is unlikely that the difference in response rate soly can be attributed to an additive effect, i.e. some patients responding to chemotherapy and some to HD-MPA. However, it should be kept in mind that most receptor assays were undertaken with tissue from the primary tumour and that receptor instability could imply that some metastases were hormone receptor positive. Likewise, the receptor status is somewhat imbalanced in the two groups with a "tendency" to more hormone receptor containing cases in the HD-MPA group although levels are low and by definition "receptor negative".

Thus the present study provides evidence that in concordance with experimental preclinical studies an interaction between chemotherapy and HD-MPA may exist resulting in an increased response rate. Side effects from MPA were substantial and the survival data are of great concern. After the present trial had been closed, we became aware of studies by Shaikh *et al.* [7, 8] that support the experimental data produced by Formelli *et al.* [2]. They found that MPA could increase the response to methotrexate, vincristine and doxorubicin of human breast cancer cells and this effect was independent of its growth inhibitory action, i.e. cells resistant to the growth inhibitory

action of MPA also exhibited progestagen/drug synergism. The same group also performed a non-randomised study [9] among patients with advanced breast cancer. They were treated with cyclical sequential administration of an oestrogen, a progestagen and two alternate combinations of cytotoxic drugs. In the 34 patients who completed three double cycles of treatment they obtained an impressive response rate of 91%. The high response rate found in the present trial support these data. The toxicity from high doses of MPA is of concern, however, and lower doses should be considered in future trials.

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Metastatic Ovarian or Colonic Cancer: A Clinical Challenge

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Clinical problems arise when histology is unable to differentiate between an ovarian carcinoma infiltrating into the rectosigmoid region and a colonic cancer with ovarian metastases. To evaluate the discriminative value of immunohistochemistry we studied four groups: (A) ovarian carcinoma (n = 21), (B) ovarian carcinoma with sigmoid stenosis (n = 18), (C) colonic carcinoma (n = 20) and (D) a group in which the differential diagnosis was a problem (n = 19). Paraffin sections stained with a panel of monoclonal antibodies revealed specific patterns: in group A and B a negative Parlam-4 and positive OC-125; in group C the opposite; in group D the 'colonic' pattern in 15 cases, and the 'ovarian' pattern in only 2. The clinical diagnosis in group D during follow-up was ovarian carcinoma in 7, colonic carcinoma in 8, double tumour in 1 and still unknown in 3. This was based on high levels of serum tumour markers such as carcinoembryonic antigen (n = 5) and CA-125 (n = 4), laparotomy (n = 4), autopsy (n = 1), barium enema and/or endoscopy (n = 5). The response to chemotherapy in group D was extremely poor.
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INTRODUCTION

THE AETIOLOGY of a tumour mass in the lower abdomen is sometimes difficult to establish both on clinical findings and histology. The diagnosis of ovarian cancer infiltrating the rectosigmoid region implies long-term aggressive chemotherapy and a fair prognosis, whereas advanced colonic cancer implies the availability of less effective chemotherapy and a poor prognosis. There are many reports dealing with ovarian metastases derived from colorectal, breast or gastric carcinoma [1, 2], sometimes appearing after a relatively long interval following surgery [3]. Only a few papers describe the diagnostic problem of a colorectal cancer presenting as an ovarian tumour mass [4]. A clear diagnostic approach and therapeutic policy is lacking. Therefore, we evaluated the discriminative value of immunohistochemistry on the impact of response to chemotherapy.

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PATIENTS AND METHODS

In 19 patients (median age 56 years, range 38–72) seen at the Netherlands Cancer Institute from 1979 to 1986 it was difficult